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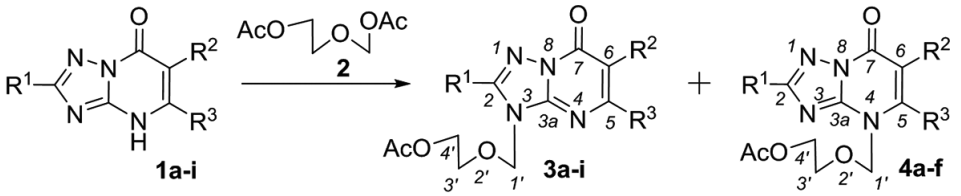
Synthesis of acyclic nucleoside analogues by one-step Vorbrüggen glyco-sylation of 1,2,4-triazolo[1,5-a]pyrimidine-7-ones

New analogues of acyclovir have been prepared by reacting 1,2,4 -triazolo[1,5-*a*]pyrimidin-7-ones **1a-i** and (2-acetoxyethoxy)methyl acetate **2** in the presence of trimethylsilyl trifluoromethanesulfonate as a catalyst. The interaction between the compounds **1a-e** and **2** has led to a mixture of N3 and N4 isomers. In contrast, the reaction of compounds **1g-i** and **2** proceeded selectively to form N3 isomers. In the case of compounds **1a-c** the predominant product is the one with the acyclic moiety in azine ring (N4 isomer). Interaction between **1d-f** and **2** has led to mixtures comprising mainly N3 isomer. It has been found that the ratio of glycosylation products **1** and **2** are thermodynamically controlled. The structure of the obtained compounds has been proved by ^{1}H, ^{13}C, two-dimensional ^{1}H-^{13}C NMR spectroscopy and X-ray analysis.

1,2,4-Triazolo[1,5-*a*]pyrimidines derivatives are the basis of many biologically active compounds[1,2], and their N-substituted derivatives can be used to create antiviral and antitumor compounds[3,4]. Considering that the therapeutic potential of nucleoside analogues based on 1,2,4-triazolo[1,5-*a*]pyrimidine-7-ones, the development of effective synthetic procedures has become an actual task. As a continuation of our studies in the search for new inhibitors of the replication of herpes simplex virus, we have synthesized a series of new acyclic nucleoside analogues 3a-i and 4a-f on the basis of 1,2,4-triazolo[1,5-*a*]pyrimidines. Reaction of 1,2,4-triazolo[1,5-*a*]pyrimidine-7-ones 1a-i with (2-acetoxyethoxy) methyl acetate in the presence of trimethylsilyl trifluoromethane sulphonate as a catalyst resulted in alkylated products 3 and 4. In the case of compounds



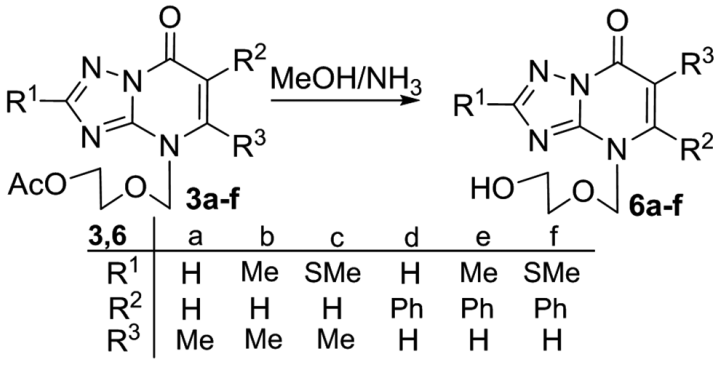
1a-c in the reaction mixture, N3 derivatives of 3a-c usually predominate. In the case of compounds 1d-f, conditions for selectively produce both N3 and N4 derivatives have been chosen. 1g-i gives only N3 alkylated products 3g-I (Table 1). The structure of 3a-i and 4a-f was defined on the basis of two-dimensional 1H-13C HMBC NMR experiments.

Table 1

Yield, ratio of isomers of acyclic nucleoside analogues

Yield, correlation of Heterocycle	R^1	R^2	R^3	Metod[a]	Ratio[b]	Yield (%)
1a	H	H	Me	A	62:38	56
				B	100:0	60
1b	Me	H	Me	A	51:49	59
				B	75:25	49
1c	SMe	H	Me	A	52:48	63
				B	94:6	80
1d	H	Ph	H	A	5:95	86
				B	75:25	48
1e	Me	Ph	H	A	40:60	70
				B	70:30	43
1f	SMe	Ph	H	A	4:96	59
				B	60:40	46
1g	H	H	Ph	A	100:0	39
				B	100:0	41
1h	Me	H	Ph	A	100:0	75
				B	100:0	24
1i	SMe	H	Ph	A	100:0	35
				B	100:0	34

[a] Conditions A: MeCN (7 mL), BSA (2 mmol), 1a-i (1.8 mmol), TMSOTf (2 mmol), 0.5ch; B: MeCN (7 mL), 1a-i (1.8 mmol), TMSOTf (2 mmol) 0.2ch; [b] The 3:4 ratio was determined by ^{1}H NMR.



Compounds 3a-I have been characterized by presence of cross peaks between the protone signals at C1' atom, and C2 and C3a carbon atoms. In the case of 4a-f derivatives, N4 position of acyclic fragment is confirmed by a cross peak between C5 and H1' atoms. Furthermore, for crystals of the 3d and 4d compounds X-ray diffraction analysis has been performed, which is fully consistent with NMR data.

Deprotection of the substances 3a-i and 4a-f under the action of a methanolic solution of ammonia has led to novel acyclovir analogues 5a-i and 6a-f. The cytotoxicity and antiviral activity of compounds 5a-i and 6a-f have been investigated against herpes simplex virus type I in Vero cells in accordance with the procedure [3]. The obtained compounds showed weaker activity against HSV compared to acyclovir.

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